UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty. Docket No.: MBHB 98-554)

In re Application of:	)	Examiner:
DeVringer, *et al.*	)	KISHORE, GOLLAMUDI S
	)	
Application No. 09/155,605	)	Art Unit: 1615
	)	
Filed: September 29, 1998	)	Confirmation No.: 8895
	)	
For: Instant Vesicular Product	)	
	)	

APPELLANTS' BRIEF IN SUPPORT OF THE APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

Dear Sir:

This Appeal Brief is submitted pursuant 37 C.F.R. § 41.37.

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I. REAL PARTY IN INTEREST

The real party in interest is Astellas Pharma Europea B.V., successor in interest to Yamanouchi Europe, B.V., Netherlands.

II. RELATED APPEALS AND INTERFERENCES

Applicant is not aware of any related appeals or interferences.

III. STATUS OF CLAIMS

Claims 1-9, 12-17 and 19-37 are pending, and the applicants appeal the final rejection of these claims. A clean set of the pending claims is attached in the Claims Appendix beginning at page 18.

IV. STATUS OF AMENDMENTS

The applicants believe the amendments made in the Office Action response filed March 25, 2005, were entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claims under appeal are product claims (claims 1–8, claims 28-35), process claims (claims 9-15 and 19), product by process claims (claims 20-27) and composition claims (claims 16, 36-37). Independent claim 1 is directed to a powder of reversed vesicles comprising one or more non-ionic surfactants whereby the yield of the reversed vesicles is greater when the powder is dispersed in biodegradable oil than when the same amount of reversed vesicles is prepared directly in biodegradable oil. (E.g., page 2, lines 6-14, Examples 1-8).

Dependent claims 2-8 are directed to the powder of reversed vesicles as defined in claim 1 wherein the vesicles comprise specific non-ionic surfactants. (E.g., page 2, line 15 to page 3 line 2)

Independent claim 9 is directed to the process of preparation of a compound comprising one or more non-ionic surfactants, wherein a dispersion of reversed vesicles from one or more non-ionic surfactants is made optionally with both a lipophilic stabilizing factor and a bioactive agent in an apolar vehicle, wherein the apolar vehicle selected is volatile and is subsequently removed by evaporation. (E.g. page 2, lines 6-14; page 3, lines 3-7; page 3, line 26 to page 4, lines 14; Examples 1-8.)

Dependent claim 12 is directed to the process as described in claim 9 wherein the volatile compound used in claim 9 is selected from a group consisting of silicone oils, isoparaffins and (C_1-C_4)alkyl alkanoates . (E.g., page 3, lines 13-14.)

Dependent claims 13-15 are directed to the process as described in claim 9, wherein specific conditions for using lipophilic stabilizing factor are recited, or where lipophilic stabilizing factor recited in claim 9 is water. (E.g., page 3, lines 15-25)

Independent claim 16 is directed to a composition comprising a powder of claims 1-8. (E.g., p. 4, ll. 1-5, Examples 1-8, claim 16 as originally filed).

Independent claim 17 and dependent claim 19 are directed to a process for preparation of dispersion of reversed vehicle in biodegradable oil. (E.g., page 2, lines 6-14; Examples 1-8.)

Independent claim 20 and dependent claims 21-27 are directed to a powder of reversed vescicles comprising one or more non-ionic surfactants produced by the process recited in claim 9. (E.g., page 2, line 15 to page 3 line 2; Examples 1-8.)

Independent claim 28 and dependent claims 29-35 are directed to a powder of reversed vesicles comprising one or more non-ionic surfactants, whereby the reversed vesicles of the powder can be dispersed in a polar vehicle or in the same apolar vehicle or different apolar vehicle. (E.g., page 2, line 15 to page 3 line 2; Examples 1-8.)

Lastly, dependent claims 36 and 37 are directed to composition comprising the powder according to any one of claims 20-35. (E.g., Examples 7-8, claim 16 as originally filed)

VI GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The rejections on appeal are:

(1) Rejection of claims 1-9, 12-17 and 19-37 under 35 U.S.C. §102(b) as being anticipated by EP 0521562 ('DeVringer').

(2) Rejection of claims 1-9, 12-17 and 19-37 35 U.S.C. §103 as being obvious over EP 0521562 ('DeVringer') by itself or in combination with EP 0678295 ('Citernesi'), EP 0159237 ('Lafon'), GB 2002319 ('Schneider'), JP 05194253 ('Hiroshi') by themselves or in combination.

(3) Rejection of claims 1-9, 12-17 and 19-37 35 U.S.C. §103 as being obvious over EP 0521562 ('DeVringer') in combination with US Pat. No. 5,693,516 ("Blinkovsky").

VII. ARGUMENT

A) Legal Background

1) Anticipation under 35 U.S.C. § 102(b)

To establish anticipation under 35 U.S.C. § 102 (b), each and every element as set forth in the claim should be found, either expressly or inherently described, in a prior art reference.

> According to MPEP Section 2131 paragraph 2, "*A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.*"

Furthermore, to sustain an anticipation rejection based on inherency, the inherent element must necessarily be present in the prior art, and it is incumbent on the Office to provide evidence or scientific reasoning demonstrating the allegedly inherent feature is necessarily present:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted) [...] >Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) [...]
>
> **"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art."** *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original) ..MPEP 2112 (IV) (emphasis added).

As explained more fully below, at the time the invention was made, the inherent element was not necessarily present in the prior art and, therefore, the cited reference cannot anticipate the present invention.

2) Obviousness under 35 U.S.C. § 103

To be patentable, an invention must be nonobvious (35 U.S.C. § 103(a)):

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

After more than two decades of Federal Circuit jurisprudence, the Supreme Court recently clarified its view of 35 U.S.C. § 103 and the obviousness inquiry in *KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727; 167 L. Ed. 2d 705; 2007 U.S. LEXIS 4745; 82 U.S.P.Q.2D (BNA) 1385 (April 30, 2007). The Court reaffirmed the objective standard set forth in *Graham v. John Deere Co. of Kansas City,* 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966):

> Under *§ 103*, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

While the Court rejected a rigid application of the so-called TSM test (teaching-suggestion-motivation) devised by the Federal Circuit, it acknowledged that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis. *KSR*, 127 S. Ct. at 1741; *see also, Takeda Chem. Indus. v. Alphapharm Pty., Ltd.,* 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007). The Federal Circuit noted in *Takeda Chem. Indus.* that "[a]s long as the test is not applied as a 'rigid and mandatory' formula, that test can provide 'helpful insight' to an obviousness inquiry." 83 U.S.P.Q.2d at 1174.

The Court did, however, discuss some factors to consider in the obvious analysis, recognizing that "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.* at 1741. But, reiterating prior holdings, the Court stated that merely identifying elements of an invention in the prior art is insufficient; more is required to establish obviousness. *Id.* ("As is clear from cases such as *Adams*, a patent composed of several elements

is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.")

The Court considered predictability an important factor in the obvious analysis. In fact, the Court found obviousness in *KSR* because "there is a design need or market pressure to solve a problem [i.e., a reason] and there are a finite number of identified, predictable solutions." *See id.* at 1732 (*emphasis added*). In several other instances the Court further stated that a combination of elements may be obvious if their combination yields a predictable result:

> The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.

Id. at 1739 (*emphasis added*). The Court also stated:

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, *§ 103* likely bars its patentability.

Id. at 1740 (*emphasis added*).

> [I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* and *Anderson's-Black Rock* are illustrative -- a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

Id. (*emphasis added*). As explained below, no such predictability in achieving the results of the presently claimed invention was possible at the priority date.

The Court also considered the forces driving innovation as important in the obvious analysis ("design incentives and other market forces can prompt variations of [a work]"):

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *Id.* at 1740-41 (emphasis added).

> Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *Id.* at 1741 (emphasis added).

As explained more fully below, at the time the invention was made, there were no forces inducing one of ordinary skill in the art to make the present invention.

Finally, other factors the Court reiterated as important in the obviousness analysis are teachings away from the claimed invention and the prohibition against hindsight reconstruction of it. "When the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). And, while cautioning against "[r]igid preventive rules that deny fact-finders recourse to common sense," the Court nevertheless reiterated its holding in *Graham*, cautioning the fact-finder against falling prey to "the distortion caused by hindsight bias" and "*ex post reasoning*." *KSR*, 127 S. Ct. at 1742 (citing *Graham*, 383 U.S., at 36, "'warning against a "temptation to read into the prior art the teachings of the invention in issue' and instructing courts to 'guard against slipping into the use of hindsight.'").

These factors have subsequently been interpreted by the Federal Circuit on several occasions. For example, the Federal Circuit confirmed that, following *KSR,* the law still requires that obviousness be established by demonstrating that the prior art provides reasons to make the particular invention and not merely general guidance. In *Pharmastem Therapeutics, Inc. v. Viacell, Inc.,* the Federal Circuit stated, "an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." 83 U.S.P.Q.2d 1289, 1350 (Fed. Cir. 2007) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

Applying the framework of *KSR* in *Pharmastem Therapeutics,* the Federal Circuit held that (a) it is necessary to demonstrate that the prior art provides reasons to make the particular invention and not merely general guidance before finding obviousness and (b) "an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). Therefore, the mere fact that certain approaches can be undertaken does not constitute a legally sufficient reason to combine the known elements in an obviousness inquiry.

The Foregoing Is Consistent with the Patent Office's guidelines regarding the obviousness analysis following *KSR* (Fed. Reg. 57,526 (2007)).

B) Discussion

1. The time the invention was made

The application claims priority to European application EP 96201290.2 filed on May 10, 1997, and for the purposes of this appeal the applicants rely on this date of invention. Doing so, however, is not an admission that an earlier date of invention cannot be establish, and the applicants reserve the right to demonstrate an earlier date of invention should it ever be necessary.

2. The level of ordinary skill in the art

For the purposes of this application, the applicants submit that the level of ordinary skill in the art is a chemist/biochemist having a working knowledge of reversed vesicles and a process of preparing such vesicles. Such a person would be aware of the state of reversed vesicle technology as of the priority date of current invention and have the ability to read and understand the scientific literature regarding various vesicle technologies.

3. Anticipation under 35 U.S.C. §102(b)

Claims 1-9, 12-17 and 19-37 are rejected for being anticipated by DeVringer.

DeVringer is relied upon, for its teaching of a form of a reversed powder. The Office alleged in the last Office Action that DeVringer teaches the present reverse vesicles containing sucrose fatty acid esters and an apolar vehicle, which is a silicone oil or isoparaffin, and further containing a lipophilic stabilizing factor such as cholesterol and an active agent. The Action further alleges that DeVringer teaches a process of preparation that involves making a dispersion of reversed vesicles from non-ionic surfactants and active agent in an apolar (non-polar) vehicle such as volatile silicone oil and removing the non-polar vehicle (abstract, col 5 line 49 to col 12 line 56, Examples and claims). In addition, the Action states, "Although *EP [DeVringer] does not explicitly teach that the preparation is in the form of a powder*, since it teaches on col. 12, lines 55-56, the removal of the non-polar vehicle (volatile silicon oil), *the teachings of a powder form of the preparation are implicit in the reference*."

The applicants disagree. DeVringer merely instructs to "remove the non-polar excipient(s) to obtain an instant preparation," but it neither removes the non-polar excipient nor

teaches a method for removing non-polar excipient that one skilled in the art would have recognized would result in the instantly claimed powder of reversed vesicles. Consequently, DeVringer cannot anticipate the present claims because the instantly claimed powder of reversed vesicles is not necessarily present.

The applicants maintain that the Office has not provided evidence or scientifically based reasoning that as of the time of filing the present invention one of ordinary skill in the art would have necessarily known of and employed a method of removing non-polar vehicles that would necessarily lead not merely to a powder, but to a powder of reversed vesicles having the properties recited in the present claims. Without such a showing, this rejection cannot stand.

Ex parte Levy (cited *supra*) is particularly relevant to the instant situation. In *Ex parte Levy*, the disputed claims had been rejected over a reference cited to inherently disclose the claimed product. However, the rejection was reversed by the Board of Patent Appeals and Interferences. Therein, the reference was found to be lacking in that it

> ...does not provide any working example revealing the process conditions employed to produce the catheter balloon. We have *only* a general invitation to employ "injection blow molding."

Id.. at 1464 (emphasis in original). In the instant case, as in *Ex parte Levy,* there is only a teaching to do something but not of how to do it in a way that yields the claimed product.

It cannot be assumed that methods that may be viable for producing powders of vesicles, micelles, or reverse micelles would be applicable to producing the presently claimed powder of reverse vesicles due to the non-trivial differences in composition and structure of each with respect to **reverse vesicles** *(vide infra)*. Importantly, not every method of removing the non-polar vehicle from the various dispersions of DeVringer will result in a powder as presently claimed. That is, a powder as presently claimed would not necessarily result from removing the non-polar vehicle in the preparations of DeVringer.

Furthermore, the applicants note that DeVringer merely recites a process that includes removing the non-polar vehicle from a dispersion of vesicles or polymerized vesicles to obtain an instant preparation. DeVringer does not disclose the instant preparation itself.

In addition, DeVringer does not anticipate the present claims because it does not contain an enabling disclosure. It is settled law that a prior art reference cannot anticipate if it is not enabling or enabled. *E.g.*, MPEP § 2121.01. DeVringer discloses dispersions of reversed vesicles prepared from different types of vesicle-forming compounds and apolar carrier materials.

Although the document in column 12, lines 55-56, mentions that the non-polar excipient(s) is to be removed to obtain an instant product, there is no teaching or even suggestion of how to do it, let alone a teaching of how to do it in a manner that would result in a powder of reversed vesicles. DeVringer teaches a number of different surfactants (non-ionic, anionic, cationic, amphoteric and other suitable ones) in combination with different non-polar vehicles, and lipophilic and hydrophilic stabilising factors were mentioned to be useful for the preparation of stable dispersions of reversed vesicles. Despite the fact that in some of these examples a volatile silicon oil was used as the non-polar vehicle, there are no teachings as to how to remove such a vehicle in a way that would lead to the presently claimed compositions. DeVringer disclosed stable dispersions of reversed vesicles in a non-polar phase, but neither it nor other art available at the priority date of the present application taught how to remove the external phase. Contrary to vesicular systems known at the time of filing the present application, the external phase consisted of a **non-polar** vehicle, **not a polar** vehicle. Conventional techniques for removing a polar vehicle from vesicular systems cannot be applied without further experimentation in reversed vesicular systems. Furthermore, the ordinary artisan would not know what would happen to the physical structure of the vesicles on removing the non-polar vehicle and would not know about the properties of the residue after removing the non-polar phase.

Finally, the Office provides support for the state of art at the time of filing the present application and states that the art cited under 103 section shows that one of skill in the art would have known of and employed a method of removing non-polar vehicles that would necessarily lead to not merely to powder but to powder of properties as recited current claims. The Office asserts that additional art cited under 103 section shows that preparation of liposomal particles (reversed vesicles) could be reconstituted into liposomes again upon addition of a medium.

According to MPEP 2131.01,

> Normally, only one reference should be used in making a rejection under 35 U.S.C. 102. However, a 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to:
> (A) Prove the primary reference contains an "enabled disclosure;"
> (B) Explain the meaning of a term used in the primary reference; or
> (C) Show that a characteristic not disclosed in the reference is inherent.

As discussed under Obviousness section below, the cited references do not fulfill any of these purposes. More specifically, the cited references relate to a completely different technology from that used in the presently claimed invention, i.e., powder of reversed vesicles and method of

production of such powders; the teachings of these cited references cannot be applied to technology of current invention. Hence, the additional cited references do not (1) prove enablement of DeVringer, or (2) explain meaning of a term used in DeVringer, or (3) prove an element missing in DeVringer as being inherent.

In conclusion, each element of the presently rejected claims is not disclosed by DeVringer as DeVringer neither inherently discloses nor enables the instantly claimed powder of reversed vesicles. Consequently, the present rejection of claims 1 – 9, 12 – 17, and 19 – 37 under 35 USC 102(b) is improper, and the Applicants respectfully request its reconsideration and withdrawal.

4. Obviousness under 35 U.S.C. §103

Claims 1-9, 12-17 and 19-37 are rejected for being obviated by DeVringer by itself, or in combination with Citernesi, Lafon, Schneider and Hiroshi by themselves or in combination. Furthermore, claims 1-9, 12-17 and 19-37 are rejected for being obvious by DeVringer in combination with Blinkovsky.

i. DeVringer

Applicants have discussed teachings of DeVringer in section under anticipation section above.

ii. Citernesi and Schneider

Citernesi, although related to vesicular dispersion preparations, teaches a composition containing a **polar** external phase and **not a non-polar** phase, as presently claimed. Citernesi relates to a completely different vesicular technology compared to the present claims. Citernesi is concerned with how to load an active principal into liposomes. It is not concerned with increasing the amount of the liposome vehicle, let alone reversed vesicles in a non-polar vehicle. Citernesi relates to providing a method to manufacture liposomes (vesicles in a polar vehicle) exhibiting a high drug content by the formation of a drug-phospholipid complex in an organic solvent first, removing the organic solvent, and then adding the polar vehicle to the residue thus obtained.

Schneider, like Citernesi, although related to vesicular dispersion preparations, also teaches composition containing a **polar** external phase, **not a non-polar** phase. Schneider, aims at providing a solution for the short shelf life of liposomes (vesicles in a **polar** vehicle) by

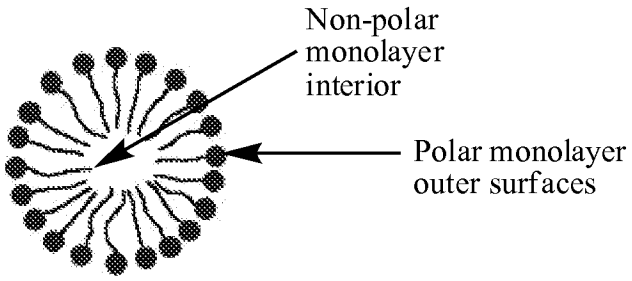
providing a process for the dehydration of the liposomes – by lyophilization in conjunction with the addition of a hydrophilic compound - to obtain a powder that can be stored for longer periods and from which, together with an aqueous medium, a liposome dispersion can be re-constituted. However, during lyophilization about 30% of the liposomes were destroyed and therefore there is a decrease in percent yield of liposomes. As Schneider deals with liposomes in a polar medium (rather than reversed vesicles in a non-polar medium) and teaches a loss of 30% of the liposomes, one of ordinary skill in the art seeking to improve the percent yield of reversed vesicles in a non-polar vehicle would not be inclined to apply the teachings of this document to this problem.

As illustrated in both Schneider and Citernesi, techniques for removing an external vehicle are commonly applied to systems wherein the external phase comprises water (*i.e.*, an aqueous, polar system). Such an external phase clearly does not meet the requirements of the instant claims for a non-polar excipient or mixture of non-polar excipients. One skilled in the art would not have any expectation of success or predictability in applying any methodology related to such aqueous systems to the instant non-polar systems, and the Office has identified none.

iii. Blinkovsky

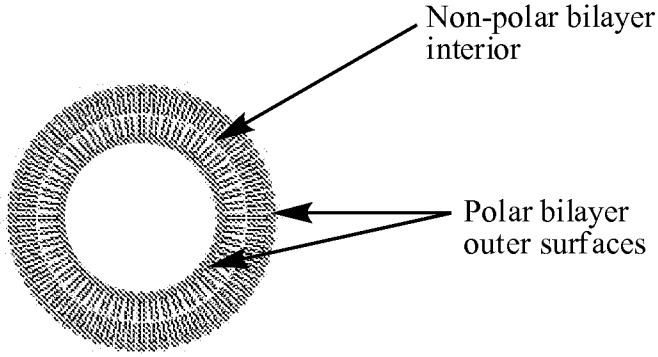
The Applicants note that DeVringer (as discussed above) is concerned with the production of dispersions of ***vesicles*** while Blinkovsky is concerned with (a) a process for preparing a ***reverse micelle*** solution from a surfactant, a protein in aqueous solution, and a water immiscible organic solvent, and evaporating the solution to dryness and (b) the product obtained according to this process (see Abstract; and Column 1, ll. 47 - 52). Therefore, one skilled in the art would not have considered combining the teachings of DeVringer with Blinkovsky because they are concerned with fundamentally different problems and are, therefore, non-analogous art. MPEP 2141.01(a).

One skilled in the art would readily recognize that micelles and vesicles, and the reversed forms of each, are fundamentally different entities. A "micelle" is an aggregate formed by a surfactant in solution such that, when formed in a polar environment (*e.g.*, water), the non-polar portion of the surfactant is in the interior of the aggregate and the polar portion is on the exterior – the interior of the aggregate is non-polar, while the exterior is polar:



For a reversed micelle, the interior of the aggregate is polar, while the exterior is non-polar.

In contrast, a "vesicle" is a closed container (in simplest terms, a sphere) defined by a bilayer formed by surfactants where the outer surfaces of the bilayer contain the polar portion of the surfactant and interior of the bilayer contains the non-polar portions of the surfactant:



When formed in a polar environment (*e.g.*, water), both the interior and exterior of a vesicle are polar. For a reversed vesicle, the interior of the bilayer forming the vesicle is polar, and outer surfaces of the bilayer are non-polar; both the interior and exterior of a reversed vesicle are non-polar.

Such definitions for micelles and vesicles are familiar to those skilled in the art; for example see page 80 of Kunieda *et al.,* "Formation and Structure of Reverse Vesicles," in Rosoff, ed. *Vesicles*, Marcel Dekker: New York, 1996, pp. 79-103 ("Kunieda"). A copy of Kunieda is included in the Evidence Appendix section. Note that page 80 (under "I. Introduction" in the first and second paragraphs) describes that surfactant molecules in a solvent can aggregate to form a variety of structures, including micelles, reverse micelles, and bilayers. The size and shape of these self-organizing structures in ternary water/surfactant/oil systems is dictated by such parameters as temperature, pressure, concentration and the interactions between surfactant, water and oil molecules. Figure 2 on page 83 shows a phase diagram illustrating the different physical systems observed at different temperatures dependent on the concentration of

oil/water; Figure 3 on page 85 show phase diagrams illustrating the different physical systems observed dependent on the concentration of the component water/surfactant/oil. Explanatory notes can be found for Figure 2 on page 82 (starting in second paragraph under "II. Surfactant phase behavior and self-organizing structures") and for Figure 3 on page 84 (starting in second full paragraph).

Further, Blinkovsky provides its own definition for the term "reverse micelles solution" (Column 2, ll. 1 - 4): a water-in-oil microemulsion comprising droplets having a size of between 0.0015-0.2 μm. Blinkovsky distinguishes a reverse micelle solution from a "reverse phase emulsion," which is a water-in-oil emulsion which has a droplet size of 0.2-100 μm (Column 2, ll. 5-9). According to Blinkovsky, these two categories are also distinguished by appearance (turbid for a reverse phase emulsion, transparent for a reverse micelle solution), and thermodynamic stability (unstable for a reverse phase emulsion, stable for a reverse micelle solution). A reverse phase emulsion will not provide the same results as a reverse micelle solution, as shown in Blinkovsky's examples in Column 2, ll. 9-15.

In view of Blinkovsky's own definitions, it is also clear that a reversed micelles solution is distinct from the reversed vesicles dispersion product according to the present invention. The dispersion of reversed vesicles of the instant claims, as assessed with polarized light microscopy, exhibit Maltese crosses (as a parameter for vesicles) and the particle size of the vesicles ranged from 1 - 16 μm (Example 6 in connection with 5) to 120 - 5138 μm (Example 7 in connection with 5), which are quite distinct from the 0.0015-0.2 μm size for reverse micelles solutions as taught by Blinkovsky.

Finally, in the method as described by Blinkovsky, it is required that a reverse micelle system be formed by a protein, an organic solvent, water and a surfactant. According to the instant claims, reversed vesicle dispersions are prepared by mixing a surfactant, a non-polar phase and optionally a lipophilic and/or hydrophilic stabilizing factor and bio-active agent. The product obtained by evaporating the transparent solution representing the reverse micelles system according to Blinkovsky ***is a soap-like solid or viscous liquid*** (Column 3, ll. 26-27), and therefore ***not a powder***, which is the product obtained by the process according to the instant claims.

The state of the art at the time of filing of the instant application with respect to reverse vesicles is reflected by the enclosed Kunieda reference. On page 80, third paragraph, Kunieda

states that until recently [1996], little attention had been paid to reverse vesicles. It is significant to note that Kunieda describes various reverse vesicular systems (starting at page 87 under B.), but notes that only few combinations resulting in reverse vesicular systems had been investigated (paragraph bridging pages 88 and 89). In particular, under "IV. Reverse vesicles in a sucrose monoalkanoate system," reverse vesicular systems in an alkane or a combination thereof with an alkanol are extensively described. Under "V. Methods to produce reverse vesicles," two methods are described to obtain a dispersion of reverse vesicles in decane.

From Kunieda, it becomes clear that (in 1996, at least) reverse vesicular systems were a developing field of research. Kunieda's failure to mention either reverse vesicles in a biodegradable oil or the preparation of powders comprising reverse vesicles suggests that little or nothing of importance had been published regarding these systems; such evidence indicates that the presently claimed powders and methods for obtaining dispersions of reverse vesicles in biodegradable oils were not yet contemplated. The teachings of Blinkovsky, both with respect to a manufacturing method for ***reverse micelles*** and for the product obtained after removing the external phase are not similar to the instant claims directed to ***reversed vesicles***.

iv. Lafon and Hiroshi

Lafon (micelles) and Hiroshi (reverse micelles) relate to a totally different physical systems having different properties from reversed vesicular systems. The differences between micelles and vesicles has been previously discussed (see, *e.g.* Blinkovsky, Column 2, ll. 2 – 15; and the previous discussion of the differences between micelles and vesicles). One skilled in the art would not combine the teachings of such non-analogous art; nor would one skilled in the art have any expectation of success in applying any methodology related to micellar systems to the instant vesicular systems.

In light of discussion above, DeVringer's (at Column 12, ll. 55-56) teaching of removal of the non-polar excipient was merely mentioned as a possible further production step. DeVringer does not specify any enabling method to remove the excipient, any result of such a removal (*i.e.*, no examples), nor any advantage or motivation why such production step should be taken, let alone whether or not this step would be feasible. Neither DeVringer nor the other cited art alone or in combination provide a reason to remove the non-polar excipient of DeVringer in a manner (e.g., protocol, including conditions and operational parameters) that would result in the presently claimed

powders, nor any teachings that would have made obtaining the presently claimed reverse vesicle powders predictable.

In addition, none of the other cited references, alone or together with each other and or DeVringer, show that it was desirable or even possible to obtain the presently claimed powder of reversed vesicles. The attainment of the presently claimed powder was not predictable from the prior art, an element necessary for finding obviousness under *KSR*. All the art other than DeVringer generally deals with systems other than reversed vesicles, and, as described above, because of the different physicochemical properties of such systems, the teachings of these prior art documents are not applicable to reversed vesicle systems. Furthermore, as evidenced by Kunieda, the knowledge of reverse vesicular systems was still in a nascent stage of the time of the invention and, accordingly, there was little, if any, guidance for those of ordinary skill in the art.

None of the cited documents, alone or in combination, would have provided the person of ordinary skill in the art any teachings to bridge the gap between the dispersions of reversed vesicles in DeVringer and the powders of the instant claims.

For all of these reasons, the applicants respectfully request that the Board order the pending rejection under 35 U.S.C. § 103 withdrawn.

VIII. CONCLUSION

The applicants respectfully submit that the present claims are not anticipated by the cited reference(s) as the cited art does not teach each and every limitation of current invention, expressly or inherently.

And pursuant to *Graham* and *KSR*, the applicants respectfully submit that the present rejection of the claims as obvious is unwarranted because a) the reversed powder and the process of its preparation were unpredictable at the priority date of the claims, and b) there is no suggestion or reason to modify teachings of prior art to reach current invention.

Respectfully submitted,

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IX. CLAIMS APPENDIX

1. A powder of reversed vesicles comprising one or more non-ionic surfactants, whereby when the powder is dispersed in a biodegradable oil the percent yield of reversed vesicles is greater than when the same amount of reversed vesicles is prepared directly in the biodegradable oil.

2. A powder according to claim 1, wherein the non-ionic surfactant is a derivative of a pentose or a hexose, or an oligomer thereof.

3. A powder according to claim 2, wherein the derivative of the pentose, hexose, or oligomer thereof is a fatty acid ester.

4. A powder according to claim 3, wherein the fatty acid ester of the pentose, hexose, or oligomer thereof consists of a mono-ester of at least 50 wt% of the surfactant.

5. A powder according to claim 4, wherein the mono-ester is present in at least 70 wt% of the surfactant.

6. A powder according to claim 1, wherein the non-ionic surfactant is a fatty acid ester of sucrose.

7. A powder according to, claim 1, wherein the vesicles further contain a lipophilic stabilizing factor.

8. A powder according to claim 1, wherein the vesicles encapsulate a bio-active compound.

9. A process for the preparation of a powder comprising one or more non-ionic surfactants, which process comprises making a dispersion of reversed vesicles from one or more non-ionic surfactants and optionally both a lipophilic stabilising factor and a bioactive agent in an apolar vehicle, wherein as the apolar vehicle a volatile compound is selected which is subsequently removed by evaporation.

10-11 (canceled)

12. The process according to claim 9, wherein the volatile compound is selected from the group consisting of silicone oils, isoparaffins and (C1-C4)alkyl alkanoates.

13. The process according to claim 9, wherein a hydrophilic stabilizing factor in an amount of up to 15 wt% of the surfactant is added during the preparation of the dispersion of reversed vesicles.

14. The process according to claim 13, wherein the hydrophilic stabilizing factor is added in an amount of between 5 and 10 wt% of the surfactant.

15. The process according to claim 14, wherein the hydrophilic stabilizing factor is water.

16. A composition comprising a powder according to any one of claims 1-8.

17. A process for the preparation of a dispersion of reversed vesicles in a biodegradable oil, wherein the powder according to any one of claims 1-8 is dispersed in the biodegradable oil.

18. (Canceled)

19. A process for the preparation of a dispersion of reversed vesicles in a biodegradable oil, wherein the product obtained from the process according to any one of claims 9 and 12-15 is dispersed in the biodegradable oil.

20. A powder of reversed vesicles comprising one or more non-ionic surfactants produced by the process according to claim 9, whereby the reversed vesicles of the powder have the same vesicular structure as in the apolar vehicle in which they were formed, and which powder of reversed vesicles can be dispersed in a polar vehicle or in the same apolar vehicle or different apolar vehicle.

21. A powder according to claim 20, wherein the non-ionic surfactant is a derivative of a pentose or a hexose, or an oligomer thereof.

22. A powder according to claim 21, wherein the derivative of the pentose, hexose, or oligomer thereof is a fatty acid ester.

23. A powder according to claim 22, wherein the fatty acid ester of the pentose, hexose, or oligomer thereof consists of a mono-ester of at least 50 wt% of the surfactant.

24. A powder according to claim 23, wherein the mono-ester is present in at least 70 wt% of the surfactant.

25. A powder according to claim 20, wherein the non-ionic surfactant is a fatty acid ester of sucrose.

26. A powder according to, claim 20, wherein the vesicles further contain a lipophilic stabilizing factor.

27. A powder according to claim 20, wherein the vesicles encapsulate a bio-active compound.

28. A powder of reversed vesicles comprising one or more non-ionic surfactants, whereby the reversed vesicles of the powder can be dispersed in a polar vehicle or in the same apolar vehicle or different apolar vehicle.

29. A powder according to claim 28, wherein the non-ionic surfactant is a derivative of a pentose or a hexose, or an oligomer thereof.

30. A powder according to claim 29, wherein the derivative of the pentose, hexose, or oligomer thereof is a fatty acid ester.

31. A powder according to claim 30, wherein the fatty acid ester of the pentose, hexose, or oligomer thereof consists of a mono-ester of at least 50 wt% of the surfactant.

32. A powder according to claim 31, wherein the mono-ester is present in at least 70 wt% of the surfactant.

33. A powder according to claim 28, wherein the non-ionic surfactant is a fatty acid ester of sucrose.

34. A powder according to, claim 28, wherein the vesicles further contain a lipophilic stabilizing factor.

35. A powder according to claim 28, wherein the vesicles encapsulate a bio-active compound.

36. A composition comprising the powder according to any one of claims 20-27.

37. A composition comprising the powder according to any one of claims 28-35.

IX. EVIDENCE APPENDIX

Kunieda *et al.,* "Formation and Structure of Reverse Vesicles," in Rosoff, ed. *Vesicles*, Marcel Dekker: New York, 1996, pp. 79-103 ("Kunieda").

X. RELATED PROCEEDINGS APPENDIX

None.